PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
F.2210/WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 03474	11/09/2000	15/09/1999
Applicant		
ASTRAZENECA UK LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   TRIAZOLOPYRIMIDINE DERIVATIVES

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. -

   [ ] as suggested by the applicant.

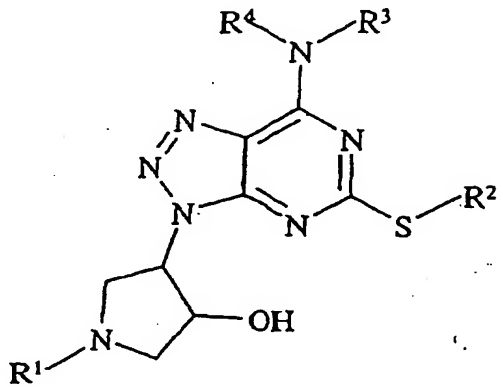
   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

Compounds of formula



(I)

and their use as anti-platelet aggregation compounds

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/03474

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/519 A61P9/00 C07D403/12 C07D207/14
C07D239/46 //(C07D487/04,249:00,239:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, WPI Data, BEILSTEIN Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 508 687 A (FISONS PLC, UK) 14 October 1992 (1992-10-14) example 9 iv ---	21
X	YEN-SHI LAI ET AL.: "Synthesis and protei kinase C inhibitory activities of lanol anaogs with replacement of the perhydroazepine moiety" JOURNAL OF MEDICINAL CHEMISTRY., vol. 40, no. 2, 1997, pages 226-35, XP002162230 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 compound 18 --- -/--	21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 March 2001	28/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/03474

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S. E. SCHAUS ET AL.: "Practical synthesis of enantiopure cyclic 1,2-amino alcohols via catalytic asymmetric ring opening of meso epoxides" JOURNAL OF ORGANIC CHEMISTRY., vol. 62, no. 12, 1997, pages 4197-4199, XP002162231 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 compounds 6 and 7 ---	21
A	WO 99 05114 A (ASTRA) 4 February 1999 (1999-02-04) claims 1,11 ---	1,9
A	WO 99 05143 A (ASTRA PHARMA PROD ;) 4 February 1999 (1999-02-04) claims 1,11 ---	1,9
X,P	WO 00 34283 A (ASTRAZENECA) 15 June 2000 (2000-06-15) example 9d ---	21
X,P	KIGUCHI ET AL.: "Radical cyclizaton in heterocyce synthesis. Part 9 : A novel synthesis of aminocyclitols and related compounds via stannyl radical cyclization of oxime ethers derived from sugars" TETRAHEDRON., vol. 56, 2000, pages 5819-5833, XP002162232 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM., NL ISSN: 0040-4020 compounds 24b and 24d -----	21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/03474

Box I Observations where certain claims w re found unsearchabl (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17 to 19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/03474

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0508687 A	14-10-1992	AT 127808 T	15-09-1995
		AU 648885 B	05-05-1994
		AU 1451992 A	02-11-1992
		CA 2107667 A	07-10-1992
		CN 1068574 A,B	03-02-1993
		CN 1120936 A	24-04-1996
		DE 69204717 D	19-10-1995
		DK 508687 T	05-02-1996
		EP 0579643 A	26-01-1994
		ES 2078654 T	16-12-1995
		FI 934366 A	05-10-1993
		WO 9217488 A	15-10-1992
		GR 3018307 T	31-03-1996
		HU 64967 A	28-03-1994
		HU 9500190 A	28-11-1995
		IE 921091 A	07-10-1992
		JP 6505987 T	07-07-1994
		MX 9201577 A	01-10-1992
		NO 933555 A	05-10-1993
		NZ 242243 A	25-06-1993
		PL 297372 A	06-09-1993
		US 5654285 A	05-08-1997
WO 9905114 A	04-02-1999	AU 8235898 A	16-02-1999
		GB 2344588 A	14-06-2000
WO 9905143 A	04-02-1999	AU 8370698 A	16-02-1999
		BR 9810802 A	12-09-2000
		CN 1270590 T	18-10-2000
		EP 0996621 A	03-05-2000
		NO 20000312 A	21-03-2000
		PL 338516 A	06-11-2000
		ZA 9806050 A	06-04-1999
WO 0034283 A	15-06-2000	AU 2016500 A	26-06-2000

CC. SCH
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EMY

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BRYANT, Tracey
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4GR
ROYAUME-UNI

CODE	DATE	NTD

ANKOM 27 AUG 2001 GIPS
DATA ENTERED
FINAL CHECK

Date of mailing (day/month/year) 16 August 2001 (16.08.01)	
Applicant's or agent's file reference F.2210/WO	**IMPORTANT NOTIFICATION**
International application No. PCT/GB00/03474	**International filing date** (day/month/year) 11 September 2000 (11.09.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address

ASTRAZENECA UK LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

RECEIVED

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address

ASTRAZENECA AB
S-151 85 Sodertalje
Sweden

State of Nationality:
State of Residence:
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:
Indication of nationality and residence of the new applicant is required.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Anman QIU
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

004217724

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
A.2210-1WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03474	11/09/2000	15/09/1999
International Patent Classification (IPC) or national classification and IPC C07D487/04		
Applicant ASTRAZENECA UK LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/03/2001	14.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Rivat, C Telephone No. +49 89 2399 2191

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03474

I. Basis of th report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-22 as originally filed

Claims, No.:

1-21 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 17-19.

because:

☒ the said international application, or the said claims Nos. 17-19 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16,20
	No:	Claims	21
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16,20-21
Industrial applicability (IA)	Yes:	Claims	1-16,20-21

No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Reference is made to the following documents :

D1: EP-A-0 508 687
D2: Yen-shi lai *et al.*, *J. Med. Chem.*, **1997**, *40(2)*, p. 226-35
D3: S. E. Schaus *et al.*, *J. Org. Chem.*, **1997**, *62(12)*, p. 4197-4199
D4: WO-A-99/05144
D5: WO-A-99/05143

An error has apparently occurred in the International Search Report. The publication number of document D4 should actually read WO-A-99/05144 (copy enclosed) instead of WO-A-99/05114.

Kiguchi *et al.*, *Tetrahedron*, **2000**, *56*, p. 5819-5833 which was cited in the ISR has been published after the priority date claimed for the present application. Since this priority is valid for the whole application, this prior art document will not be taken into account for the assessment of novelty and inventive step (R. 64(1) PCT) .

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 17-19 relate to subject-matter considered by this Authority to be covered by the provisions of R. 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1.1. Document D1 describes ATP analogs useful as P_{2T} receptor agonists/antagonists. As ATP analogs, the core structure of these compounds consists of an adenosine moiety and differs therefore from the triazolo-pyrimidin-pyrrolidine arrangement characteristic of the compounds claimed in the present application (claims 1-16 and

20). However, in example 9 of D1, an intermediate iv) is synthesized which corresponds to formula (V) of claim 21 so that claim 21 cannot be considered as new with regard to D1 (Art. 33(2) PCT).

Document D2 deals with the synthesis of balanol derivatives as well as their use as protein kinase C inhibitors. Although these derivatives are structurally different from the claimed compounds, the intermediate 18 (n=1 an X=-NCbz-, p. 228, right col., 2nd § and scheme 3) as well as the second intermediate in the synthesis of 42 (scheme 7) are both falling within the definition of formula (IV) as disclosed in claim 21 of the present application. Claim 21 is therefore lacking novelty with regard to D2 (Art. 33(2) PCT).

Document D3 reveals a synthetical pathway to cyclic 1,2-amino alcohols. Amongst others two pyrrolidine derivatives 6 and 7 (scheme 2) are disclosed which correspond to the general formula (IV) disclosed in the present application. Claim 21 is therefore lacking novelty vis-à-vis D3 (Art. 33(2) PCT).

1.2. Documents D4 and D5 disclose triazolo-pyrimidin-cyclopentane derivatives exhibiting an activity towards P_{2T} receptors. These compounds possess a core structure analog to that of the claimed compounds. However, a cyclopentane is present instead of the pyrrolidine ring characteristic of the present invention.

Since the process of synthesis disclosed in D4 and D5 also differs from the one of the present application, novelty of claims 1-16 and 20-21 is therefore established vis-à-vis D4 and D5 (Art. 33(2) PCT).

2. Documents D4 and D5, which are considered to represent the most relevant state of the art, discloses P_{2T} receptors antagonists which differ from the subject-matter of the present invention by the absence of a nitrogen atom in the cyclopentane ring.

The problem to be solved by the present invention may therefore be regarded as the provision of new triazolo-pyrimidin derivatives exhibiting an activity towards P_{2T} receptors.

According to document D4, R^1 represents preferably a propyl (p. 3, l. 25), R 2is preferably a cyclopropyl substituted by a phenyl (p. 4, l. 7-8), R^3 is preferably a hydroxy while R^4 represents preferably a hydrogen (p. 4, l. 10-11). Moreover, example 5 illustrated the combination of these different preferred embodiments so that the skilled man would have considered starting from example 5 in order to provide new compounds active on the P_{2T} receptor.

Small modifications (such as the replacement of a carbon atom by a nitrogen atom) within a known active structure are a matter of normal drug design. Starting from example 5 of D4, the skilled person would therefore regard it as a normal design option to include a nitrogen atom in the compound of example 5 described in document D4 in order to solve the problem posed. The subject-matter of claims 1-16 and 20-21 is therefore lacking an inventive step (Art. 33(3) PCT).

3. For the assessment of the present claims 17-19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

The applicant's attention is drawn to the fact that the P-document WO-A-00/34283 cited in the International Search Report (see R. 64(3) PCT) may prove relevant for the assessment of novelty when entering the European phase.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BRYANT, Tracey
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4GR
ROYAUME-UNI

Date of mailing (day/month/year)
16 août 2001 (16.08.01)

Applicant's or agent's file reference
F.2210/WO

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/03474

International filing date (day/month/year)
11 septembre 2000 (11.09.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
ASTRAZENECA UK LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
ASTRAZENECA AB
S-151 85 Sodertalje
Sweden

State of Nationality:
State of Residence:
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:
Indication of nationality and residence of the new applicant is required.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Anman QIU

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 19 June 2001 (19.06.01)	
International application No. PCT/GB00/03474	**Applicant's or agent's file reference** F.2210/WO
International filing date (day/month/year) 11 September 2000 (11.09.00)	**Priority date** (day/month/year) 15 September 1999 (15.09.99)
Applicant TEOBALD, Barry, John	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

23 March 2001 (23.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Pascal Piriou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 March 2001 (22.03.2001)

PCT

(10) International Publication Number
WO 01/19826 A2

(51) International Patent Classification[7]: C07D 487/04, A61K 31/519, A61P 9/00, C07D 403/12 // (C07D 487/04, 249:00, 239:00)

(21) International Application Number: PCT/GB00/03474

(22) International Filing Date:
11 September 2000 (11.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9903290-6 15 September 1999 (15.09.1999) SE

(71) Applicant *(for all designated States except US)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventor; and

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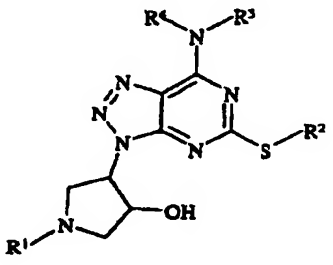
(54) Title: NOVEL COMPOUNDS



(57) Abstract: The invention provides novel hydroxypyrrolidine compounds, their use as medicaments, compositions containing them and processes for their preparation.

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NOVEL COMPOUNDS

FIELD OF THE INVENTION

The present invention provides novel hydroxypyrrolidine compounds, their use as medicaments, compositions containing them and processes for their preparation.

BACKGROUND OF THE INVENTION

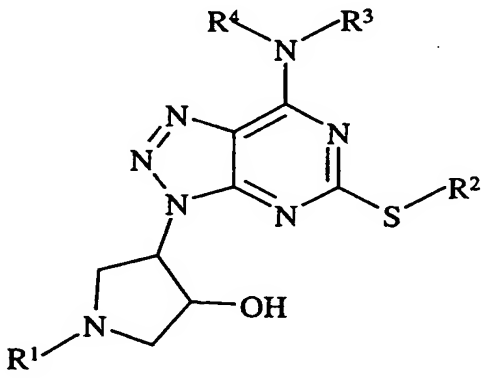
Platelet adhesion and aggregation are initiating events in arterial thrombosis. Although the process of platelet adhesion to the sub-endothelial surface may have an important role to play in the repair of damaged vessel walls, the platelet aggregation that this initiates can precipitate acute thrombotic occlusion of vital vascular beds, leading to events with high morbidity such as myocardial infarction and unstable angina. The success of interventions used to prevent or alleviate these conditions, such as thrombolysis and platelet-mediated occlusion or re-occlusion also compromises angioplasty.

A number of converging pathways lead to platelet aggregation. Whatever the initial stimulus, the final common event is a cross-linking of platelets by binding of fibrinogen to a membrane-binding site, glycoprotein IIb/IIIa (GPIIb/IIIa). The high anti-platelet efficacy of antibodies or antagonists for GPIIb/IIIa is explained by their interference with this final common event. However, this efficacy may also explain the bleeding problems that have been observed with this class of agent. Thrombin can produce platelet aggregation largely independently of other pathways but substantial quantities of thrombin are unlikely to be present without prior activation of platelets by other mechanisms. Thrombin inhibitors such as hirudin are highly effective anti-thrombotic agents, but again may produce excessive bleeding because they function as both anti-platelet and anti-coagulant agents (The TIMI 9a Investigators (1994), *Circulation* **90**, pp. 1624-1630; The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators (1994) *Circulation* **90**, pp. 1631-1637; Neuhaus K. L. et. al. (1994) *Circulation* **90**, pp. 1638-1642).

It has been found that ADP acts as a key mediator of thrombosis. ADP-induced platelet aggregation is mediated by the P_{2T} receptor subtype located on the platelet membrane. The P_{2T} receptor (also known as $P2Y_{ADP}$ or $P2T_{AC}$) is primarily involved in mediating platelet aggregation/activation and is a G-protein coupled receptor. The pharmacological characteristics of this receptor have been described, for example, in the references by Humphries et al., *Br. J. Pharmacology,* (1994), **113**, 1057-1063, and Fagura et al., *Br. J. Pharmacology* (1998) **124**, 157-164. Recently it has been shown that antagonists at this receptor offer significant improvements over other anti-thrombotic agents (see *J. Med. Chem.* (1999) **42**, 213). There is a need to find P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) antagonists as anti-thrombotic agents.

DESCRIPTION OF THE INVENTION

In a first aspect the invention provides a compound of formula (I):



(I)

wherein:

R^1 is H, CH_2R^5 or COR^6;

R^2 is alkyl C_{1-6} or alkenyl C_{1-6}, optionally substituted by one or more groups selected from alkyl C_{1-6}, halogen;

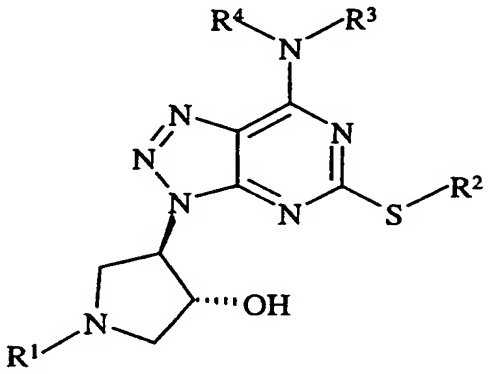
R^3 is cycloalkyl C_{3-8}, optionally substituted by R^7;

R^4 is H or alkyl C_{1-6}, optionally substituted by one or more halogens;

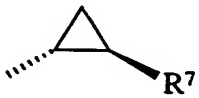
R^5 is H, phenyl or alkyl C_{1-6}, optionally substituted by halogen, OR^8, phenyl;
R^6 is OR^9 or alkyl C_{1-6}, optionally substituted by one or more groups selected from halogen, OR^{10}, phenyl;
R^7 is phenyl, optionally substituted by one or more groups selected from alkyl C_{1-6}, halogen, OR^8;
R^8, R^9 and R^{10}, are independently H or alkyl C_{1-6}, optionally substituted by one or more groups selected from halogen or alkyl C_{1-6};

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

Preferably the compound of formula (I) has the following stereochemistry:



(Ia)

Where R^3 is  the stereochemistry is preferably 

Preferably R^1 is H, CH_2Ph, CH_2CH_2OH, or CO_2tBu.
Preferably R^2 is n-Pr.
Preferably R^3 is cycloalkyl C_{3-8} substituted by phenyl.
Preferably R^4 is H or methyl.

Compounds of the invention include:

[3*R*-[3α,4β(1*R**,2*S**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol;

[3*S*-[3α,4β(1*S**,2*R**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester;

[3*S*-[3α,4β(1*R**, 2*S**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester;

[3*S*-[3α,4β(1*S**,2*R**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol;

[3*R*-[3α,4β(1*R**,2*S**)]]-4-[7-[*N*-Methyl-*N*-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol;

[3*R*-[3α,4β(1*R**,2*S**)]]-1-Hydroxyethyl-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol;

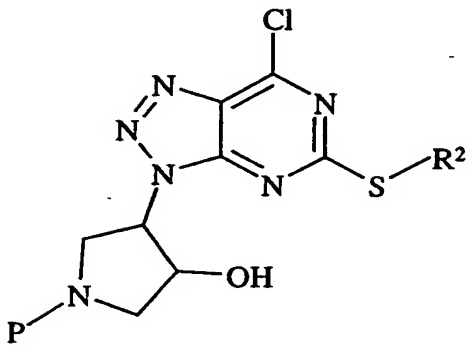
[3*R*-[3α,4β(1*R**,2*S**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-(phenylmethyl)-3-pyrrolidinol;

[3*R*-[3α, 4β(1*R**,2*S**)]]-1-Acetyl-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol.

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

The invention further provides a process for the preparation of a compound of formula (I) which comprises:

a. For compounds of formula (I) where R^1 is H, reacting a compound of formula (II):

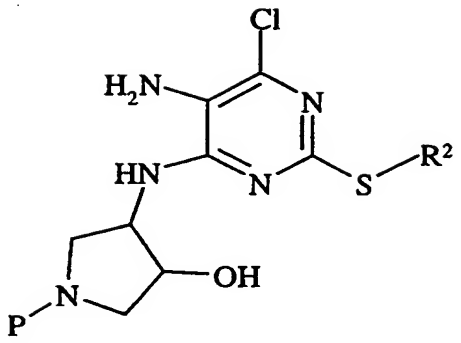


(II)

wherein R^2 is as defined above and P is a protecting group, preferably t-BuOCO, with R^3R^4NH, wherein R^3 and R^4 are as defined in (I), and a base, preferably triethylamine or *N,N*-diisopropylethylamine, in the presence of an inert solvent preferably acetonitrile, preferably at a temperature between about 20 °C and about 100 °C and optionally thereafter removing any protecting groups.

Examples of protecting groups include t-BuOCO and CH_2Ph. Protecting groups can be added and removed using known reaction conditions. The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

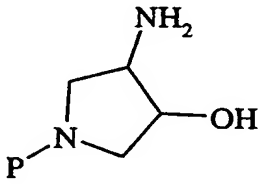
A compound of formula (II) can be prepared by diazotizing a compound of formula (III):



(III)

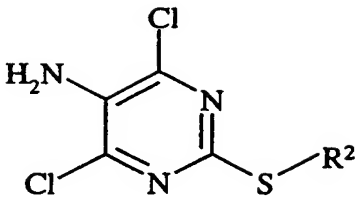
where R^2 and P are defined above, and where necessary other reactive groups might also be protected, with a C_{1-6} alkyl nitrite, preferably iso-amylnitrite in the presence of an inert solvent preferably acetonitrile at a temperature of between about 20 and about 80°C, or with an alkali metal nitrite, preferably sodium nitrite, under aqueous acidic conditions, preferably aqueous hydrochloric or acetic acid and preferably at a temperature between about 0°C and about 20°C.

A compound of formula (III) can be prepared by reacting a compound of formula (IV):



(IV)

wherein P is a protecting group, with a compound of formula (V):

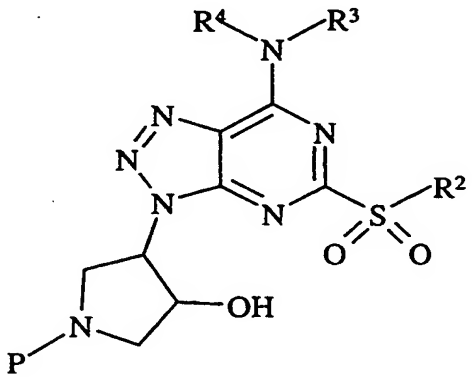


(V)

wherein R^2 is as defined in formula (I) and is preferably n-propyl. The reaction is carried out in the presence of a base, preferably triethylamine or *N,N*-diisopropylethylamine, in an inert solvent preferably *N,N*-dimethylformamide or n-butanol, at a temperature between about 100°C and about 150°C.

The preparation of the formula (IV) racemate is described in Okada et al., Chem. Pharm. Bull. (1993), **41**, 132-8; the preparation of formula (IV) enantiomers is described in Schaus, et al., J. Org. Chem. (1997), **62**, 4197-9; the preparation of a compound of formula V (R^2 is n-propyl) is described in EP 508687.

Compounds of formula (I) where R^2 is other than n-propyl are prepared by displacement of the sulphone group from a compound of formula (VI):



(VI)

where R^2 is n-propyl, P, R^3 and R^4 are defined above, using either a sodium alkylthiolate (R^2SNa) in the presence of an inert solvent, preferably *N,N*-dimethylformamide, preferably at a temperature between about 0°C and about 50°C or sodium hydrosulphide (NaSH), in the presence of an inert solvent preferably *N,N*-dimethylformamide. The latter reaction is followed by alkylation with an alkyl halide (R^2X, where X is a leaving group preferably bromide or iodide), preferably at a temperature between about 0°C and about 50°C and optionally thereafter removing any protecting groups.

The preparation of the compound of formula (VI), where R^2 is n-propyl, is preferably carried out by reacting a compound of formula (I), where R^1 has been protected as described above, with a peracid, preferably *m*-chloroperbenzoic acid, in the presence of an inert chlorocarbon solvent such as dichloromethane or a mixture of dichloromethane and methanol, at a temperature between about 0 °C and about 50 °C.

b. For compounds of formula (I) where R^1 is CH_2R^5, where R^5 is defined in formula (I), the reaction scheme outlined in a. above is followed by reductive amination using an aldehyde (R^5CHO) and a reducing agent, preferably sodium triacetoxyborohydride, and optionally thereafter removing any protecting groups. The reductive amination reaction is preferably carried out in the presence of an inert solvent preferably *N,N*-dimethylformamide, tetrahydrofuran or a mixture of acetonitrile and *N*-methylpyrrolidone and preferably at a temperature between about 0 °C and about 50 °C.

c. For compounds of formula (I) where R^1 is COR^6, where R^6 is defined in formula (I), the reaction scheme outlined in a. above is followed by acylation using an acid halide (R^6COX) or anhydride ($(R^6CO)_2O$) or an acid (R^6CO_2H) in the presence of a suitable activating agent preferably *N,N'*-carbonyldiimidazole or *N,N'*-dicyclohexylcarbodiimide, and a base preferably triethylamine or *N,N*-diisopropylethylamine, and optionally thereafter removing any protecting groups. The acylation is preferably carried out in the presence of an inert solvent preferably dichloromethane, chloroform or tetrahydrofuran and preferably at a temperature between about 0 °C and about 50 °C.

Compounds of formula (II), (III), (IV) and (V) form a further aspect of the invention.

Salts of the compounds of formula (I) may be formed by reacting the free base, or a salt or a derivative thereof, with one or more equivalents of the appropriate acid (for example a hydrohalic (especially HCl), sulphuric, oxalic or phosphoric acid). The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g. water, ethanol, tetrahydrofuran, or diethyl ether, which may be removed *in vacuo*, or by freeze drying. The reaction may also be a metathetical process or it may be carried out on an ion exchange resin. The non-toxic physiologically acceptable salts are preferred, although other salts may be useful, e.g. in isolating or purifying the product.

The compounds of the invention act as P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) receptor antagonists. Accordingly, the compounds are useful in therapy, including combination therapy, particularly they are indicated for use as: inhibitors of platelet activation, aggregation and degranulation, promoters of platelet disaggregation, anti-thrombotic agents or in the treatment or prophylaxis of unstable angina, coronary revascularisation procedures including angioplasty (PTCA), myocardial infarction, perithrombolysis, primary arterial thrombotic complications of atherosclerosis such as thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease, myocardial infarction with or without thrombolysis, arterial complications due to interventions in atherosclerotic disease such as angioplasty, endarterectomy, stent placement, coronary and other vascular graft surgery, thrombotic complications of surgical or mechanical damage such as tissue salvage following accidental or surgical trauma, reconstructive surgery including skin and muscle flaps, conditions with a diffuse thrombotic/platelet consumption component such as disseminated intravascular coagulation, thrombotic thrombocytopaenic purpura, haemolytic uraemic syndrome, thrombotic complications of septicaemia, adult respiratory distress syndrome, anti-phospholipid syndrome, heparin-induced thrombocytopaenia and pre-eclampsia/eclampsia, or venous thrombosis such as deep vein thrombosis, venoocclusive disease, haematological conditions such as myeloproliferative disease, including thrombocythaemia, sickle cell disease; or in the prevention of mechanically-induced platelet activation *in vivo*, such as cardio-pulmonary bypass and extracorporeal membrane oxygenation (prevention of microthromboembolism), mechanically-induced

platelet activation *in vitro*, such as use in the preservation of blood products, e.g. platelet concentrates, or shunt occlusion such as in renal dialysis and plasmapheresis, thrombosis secondary to vascular damage/inflammation such as vasculitis, arteritis, glomerulonephritis, inflammatory bowel disease and organ graft rejection, conditions such as migraine, Raynaud's phenomenon, conditions in which platelets can contribute to the underlying inflammatory disease process in the vascular wall such as atheromatous plaque formation/progression, stenosis/restenosis and in other inflammatory conditions such as asthma, in which platelets and platelet-derived factors are implicated in the immunological disease process. Further indications include treatment of CNS disorders and prevention of the growth and spread of tumours.

In particular, the compounds of the invention are useful in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, peripheral vascular disease and stable and unstable angina, especially unstable angina.

The invention also provides a method of treatment or prevention of the above disorders which comprises administering to a patient suffering from or susceptible to such a disorder a therapeutically effective amount of a compound according to the invention.

According to the invention there is further provided the use of a compound according to the invention as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of the above disorders.

The compounds may be administered topically, e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, pills, capsules, syrups, powders or granules, or by parenteral administration in the form of sterile parenteral solutions or suspensions, by subcutaneous administration, or by rectal administration in the form of suppositories or transdermally.

The compounds of the invention may be administered on their own or as a pharmaceutical composition comprising the compound of the invention in combination with a

pharmaceutically acceptable diluent, adjuvant or carrier. Particularly preferred are compositions not containing material capable of causing an adverse, e.g. an allergic, reaction.

Dry powder formulations and pressurised HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation the compound is desirably finely divided. The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler. One possibility is to mix the finely divided compound with a carrier substance, e.g. a mono-, di- or polysaccharide, a sugar alcohol or another polyol. Suitable carriers include sugars and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound. Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, e.g. that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active compound with or without a carrier substance is delivered to the patient.

The pharmaceutical composition comprising the compound of the invention may conveniently be tablets, pills, capsules, syrups, powders or granules for oral administration; sterile parenteral or subcutaneous solutions, suspensions for parenteral administration or suppositories for rectal administration.

For oral administration the active compound may be admixed with an adjuvant or a carrier, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution, which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like.

Alternatively, the tablet may be coated with a suitable polymer dissolved either in a readily volatile organic solvent or an aqueous solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above mentioned excipients for tablets, e.g. lactose, saccharose, sorbitol , mannitol, starches, cellulose derivatives or gelatine. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing the compound, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

EXAMPLES

The invention is illustrated by the following non-limiting examples.

In the examples the NMR spectra were measured on a Varian Unity Inova 300 or 400 spectrometer and the MS spectra were measured as follows: EI spectra were obtained on a VG 70-250S or Finnigan Mat Incos-XL spectrometer, FAB spectra were obtained on a VG70-250SEQ spectrometer, ESI and APCI spectra were obtained on Finnigan Mat SSQ7000 or a Micromass Platform spectrometer. Preparative HPLC separations were generally performed using a Novapak® , Bondapak® or Hypersil® column packed with BDSC-18 reverse phase silica. Flash chromatography (indicated in the Examples as (SiO_2)) was carried out using Fisher Matrix silica, 35-70 μm. For examples which show the presence of rotamers in the proton NMR spectra only the chemical shifts of the major rotamer are quoted.

Example 1

[3*R*-[3α,4β(1*R,2*S**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol, trifluoroacetate salt**

a) (3*R*,4*R*)-3-[[5-Amino-6-chloro-2-(propylthio)pyrimidin-4-yl]amino]-4-hydroxy-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester

Triethylamine (18.8ml) was added to a solution of (3*R*,4*R*)-4-amino-3-hydroxy-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester (prepared as described in J. Org. Chem., **1997**, *62*, 4197 using the (*S*,*S*)(salen)Cr(III)complex) (3.63g) and 4,6-dichloro-2-propylthiopyrimidine-5-amine (prepared as described in *EP508687*) (3.56g) and the resulting mixture was heated at 100°C for 24 hours. The excess triethylamine was removed *in vacuo* and the residue was diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, dichloromethane:methanol, 97:3 as eluant) followed by trituration with diethylether/iso-hexane to give the subtitle compound (4.16g).

MS (APCI) 404 ($M+H^+$, 100%).

b) (3*R*,4*R*)-4-[7-Chloro-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-hydroxy-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester

The product from step a) (4.1g) and iso-amylnitrite (2.74ml) were heated under reflux in acetonitrile (20ml) for 1 hour. The reaction mixture was concentrated *in vacuo* and the residue purified by chromatography (SiO_2, ethyl acetate:iso-hexane, 1:4 as eluant) to afford the sub-title compound (3.32g).

MS (APCI) 415 ($M+H^+$, 100%).

c) [3*R*-[3α,4β(1*R,2*S**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester**

N,N-diisopropylethylamine (3ml) was added to a solution of the product from step b) (1.2g) and (1*R-trans*)-2-phenylcyclopropanamine, [*R*-(*R*, R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described by L. A. Mitscher *et al.*, J. Med. Chem., **1986**, *29*, 2044) (1.23g) in dichloromethane (40ml). The reaction mixture was stirred at room temperature for 16 hours then washed with water. The organic phase was washed with dilute hydrochloric acid and brine, dried and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, dichloromethane:methanol, 99:1 as eluant) to afford the sub-title compound (1.12g).

MS (APCI) 512 ($M+H^+$, 100%).

d) [3*R*-[3α,4β(1*R,2*S**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol, trifluoroacetate salt**

The product from step c) (0.54g) was dissolved in trifluoroacetic acid (22.5ml) and water (2.5ml) and the solution stirred at room temperature for 4h. The solvents were evaporated and the residue dried by azeotropic distillation with toluene (4x50ml) followed by methanol (50ml) to give a yellow foam. The crude product was triturated with diethylether (50ml) to afford a white powder that was recrystallised (ethyl acetate) to afford the title compound (0.37g) as a white solid.

MS (APCI) 412 ($M+H^+$, 100%)

NMR δH (d_6-DMSO) 9.5 (2H, br s), 9.47 (1H, d), 7.10-7.35 (5H, m), 6.28 (1H, d), 5.26 (1H, br m), 4.65 (1H, br s), 3.90 (2H, m), 3.52 (1H, d,AB), 3.3 (1H, m), 3.24. (1H, m), 2.8-3.0 (2H, t,AB), 2.13 (1H, m), 1.54 (1H, d,t), 1.47 (2H, sext.), 1.34 (1H, br q), 0.79 (3H, t).

Example 2

[3*S*-[3α,4β(1*S,2*R**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester**

a) (3*S*,4*S*)-3-[[5-Amino-6-chloro-2-(propylthio)pyrimidin-4-yl]amino]-4-hydroxy-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester

Prepared according to the method of Example 1, step a) using (3*S*,4*S*)-4-amino-3-hydroxy-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester (prepared as described in J. Org. Chem., **1997**, *62*, 4197 using a(*R*,*R*)(salen)Cr(III)complex).

MS (APCI) 404/406 ($M+H^+$), 404 (100%).

b) (3*S*,4*S*)-4-[7-Chloro-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-hydroxy-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester

Prepared according to the method of Example 1, step b).

MS (APCI) 315 ($M+H-BOC^+$, 100%).

c) [3*S*-[3α,4β(1*S,2*R**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester**

Prepared according to the method of Example 1, step c).

MS (APCI) 512 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.40 (1H, d), 7.31-7.27 (2H, m), 7.20-7.15 (3H, m), 5.78-5.76 (1H, m), 5.11-5.06 (1H, m), 4.61-4.56 (1H, m), 3.94-3.81 (2H, m), 3.69-3.62 (1H, m), 3.30-3.18 (2H, m), 3.11-2.80 (2H, m), 2.15-2.10 (1H, m), 1.73-1.23 (13H, m), 0.80 (3H, t).

Example 3

[3*S*-[3α,4β(1*R, 2*S**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester**

a) [3*S*-[3α,4β(1*R, 2*S**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester**

Prepared according to the method of Example 2, step c) using (1*S*-*trans*)-2-phenylcyclopropanamine, [*S*-(*R**, *R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described by L. A. Mitscher *et al.*, J. Med. Chem., **1986**, *29*, 2044).

MS (APCI) 512 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.40 (1H, d), 7.31-7.27 (2H, m), 7.20-7.15 (3H, m), 5.78-5.76 (1H, m), 5.11-5.06 (1H, m), 4.62-4.58 (1H, m), 3.94-3.81 (2H, m), 3.69-3.63 (1H, m), 3.30-3.18 (2H, m), 3.11-2.80 (2H, m), 2.15-2.11 (1H, m), 1.72-1.23 (13H, m), 0.80 (3H, t).

Example 4

[3*S*-[3α,4β(1*S,2*R**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol, trifluoroacetate salt**

a) [3*S*-[3α,4β(1*S,2*R**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol, trifluoroacetate salt**

Prepared according to the method of Example 1, step d) using the compound of Example 2, step c)

MS (APCI) 412 ($M+H^+$, 100%)

NMR δH (d_6-DMSO) 9.5 (2H, br s), 9.48 (1H, d), 7.10-7.35 (5H, m), 6.30 (1H, d), 5.26 (1H, br m), 4.64 (1H, br s), 3.9 (2H, m), 3.5 (1H, d,AB), 3.26 (1H, m), 3.24. (1H, m), 2.7-3.0 (2H, t,AB), 2.11 (1H, m), 1.55 (1H, d,t), 1.46 (2H, sext.), 1.34 (1H, br q), 0.78 (3H, t).

Example 5

[3*R*-[3α,4β(1*R,2*S**)]]-4-[7-[*N*-Methyl-*N*-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol, trifluoroacetate salt**

a) [3*R*-[3α,4β(1*R,2*S**)]]-3-Hydroxy-4-[7-[N-methyl-*N*-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester.**

N,N-diisopropylethylamine (0.5ml) was added to a solution of the product from Example 1 step b) (0.3g) and (1*R-trans*)-*N*-methyl-2-phenylcyclopropylamine hydrochloride (prepared as described by C. Kaiser *et al*, J. Org. Chem., **1962**, *27*, 768-773, using (1*R-trans*)-2-phenylcyclopropanamine, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described by L.A. Mitscher *et al*, J. Med. Chem., **1986**, *29*, 2044) (0.2g) in dichloromethane (20ml). The reaction mixture was stirred at room temperature for 48 hours then washed with water. The organic phase was washed with dilute hydrochloric acid and brine, dried and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, dichloromethane:methanol, 99:1 as eluant) to afford the sub-title compound (0.36g).

MS (APCI) 470 ($M+H^+$, 100%).

b) [3*R*-[3α,4β(1*R,2*S**)]]-4-[7-[*N*-Methyl-*N*-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol, trifluoroacetate salt**

A solution of the product from step a) (0.36g) in 9:1 trifluoroacetic acid:water (10ml) was stirred at room temperature for 2 hours. The solvent was removed and co-evaporated with toluene (3x). The residue was dissolved in water (20ml) and ethanol (1ml) and freeze-dried for 16 hours to give the title compound (0.33g).

MS (APCI) 426 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.33 (2H, br s), 7.29 (2H, m), 7.20 (3H, m), 6.04 (1H, br s), 5.27 (1H, m), 4.72 (1H, d), 3.84-3.97 (2H, m), 3.56 (4H, m), 3.31 (1H, d), 3.06 (3H, under DMSO), 2.43 (1H, under H_2O), 1.54-1.66 (3H, m), 1.45 (1H, m), 0.94 (3H, t).

Example 6

[3*R*-[3α,4β(1*R,2*S**)]]-1-Hydroxyethyl-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol, trifluoroacetate salt**

a) [3*R*-[3α,4β(1*R,2*S**)]]-1-[2-[(1,1-Dimethylethyl)(dimethyl)silyl]oxy]ethyl-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol.**

[[(1,1-Dimethylethyl)dimethylsilyl]oxy]acetaldehyde (*Tet. Lett.*, **1995**, *36*, 6033) (0.27g) was added to a solution of the product from Example 1 step d) (0.4g) and sodium triacetoxyborohydride (0.48g) in dry tetrahydrofuran (10ml) and the mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with water and extracted with ethyl acetate (thrice). The combined organic phase was washed with brine, dried and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, dichloromethane:methanol, 99:1 as eluant) to give the sub-title compound (0.2g).

MS (APCI) 570 ($M+H^+$, 100%).

b) [3*R*-[3α,4β(1*R,2*S**)]]-1-Hydroxyethyl-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol, trifluoroacetate salt**

Tetrabutylammonium fluoride hydrate (0.2g) was added to a solution of the product from step a) (0.2g) in dry tetrahydrofuran (10ml) and the mixture was stirred at room temperature for 16 hours. The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO_2, dichloromethane:methanol, 95:5 as eluant). Trifluoroacetic acid (22μl) was added to a solution of the resulting oil in diethylether (5ml) and the solid formed was collected by filtration to give the title compound (0.12g).

MS (APCI) 456 ($M+H^+$, 100%).

NMR δH (d_6-DMSO+D_2O) 7.31 (2H, m), 7.21 (3H, m), 5.36 (1H, br s), 4.87 (1H, br s), 4.18 (1H, m), 4.04 (1H, m), 3.82 (3H, m), 3.55 (1H, under H_2O), 3.45 (2H, m), 3.29(1H, br s), 3.02 (2H, br s), 2.22 (1H, br s), 1.58 (2H, br s), 1.50 (1H, m), 1.36 (1H, m), 0.88 (3H, br s).

Example 7

[3*R*-[3α,4β(1*R,2*S**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-(phenylmethyl)-3-pyrrolidinol, trifluoroacetate salt**

Benzaldehyde (0.1ml) was added to a solution of the product from Example 1 step d) (0.26g) and sodium triacetoxyborohydride (0.32g) in dry tetrahydrofuran (10ml) and the mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with water and extracted with ethyl acetate (thrice). The combined organic phase was washed with brine, dried and concentrated. Trifluoroacetic acid (20μl) was added to a solution of the resulting oil in diethylether (5ml) and the solvent was removed *in vacuo*. The residue was dissolved in water (20ml) and ethanol (5ml) and freeze-dried for 16 hours. Purification by chromatography (HPLC, Novapak® C18 column, 0.1% aqueous trifluoroacetic

acid:acetonitrile, gradient elution 75:25 to 0:100 over 15 minutes), followed by freeze drying gave the title compound (0.094g).

MS (APCI) 502 ($M+H^+$, 100%).

NMR δH (d_6-DMSO+D_2O) 7.53 (2H, d), 7.48 (3H, m), 7.31 (2H, m), 7.20 (3H, m), 5.34 (1H, m), 4.88 (1H, m), 4.48 (2H, q), 4.05 (1H, m), 3.90 (1H, m), 3.72 (1H, m), 3.41 (1H, m), 3.30(1H, br m), 3.01 (2H, br m), 2.21 (1H, br s), 1.50-1.56 (3H, m), 1.36 (1H, m), 0.87 (3H, br s).

Example 8

[3*R*-[3α, 4β(1*R,2*S**)]]-1-Acetyl-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol.**

A mixture of the product from Example 1 step d) (0.17g), acetic anhydride (0.046ml) and pyridine (0.078ml) in dichloromethane (3ml) was stirred at room temperature under a nitrogen atmosphere for 16 hours. The reaction mixture was diluted with water and extracted with dichloromethane (twice). The combined organic phase was washed with dilute hydrochloric acid and brine, dried and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, dichloromethane:methanol, 98:2 as eluant) followed by trituration with acetonitrile to give the title compound (0.06g).

MS (APCI) 454 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.39 (1H, m), 7.30 (2H, m), 7.19 (3H, m), 5.77-5.86 (1H, m), 5.09-5.16 (1H, m), 4.60-4.69 (1H, m), 4.00-4.13 (1H, m), 3.91 (2H, m), 3.46, 3.68 (1H, m), 3.21 (1H, br m), 2.82-2.91 (2H, m), 2.13 (1H, m), 1.98 (3H, d), 1.34-1.54 (4H, m), 0.79 (3H, t).

Pharmacological data

The preparation for the assay of the P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$)-receptor agonist/antagonist activity in washed human platelets for the compounds of the invention was carried out as follows.

Human venous blood (100 ml) was divided equally between 3 tubes, each containing 3.2% trisodium citrate (4 ml) as anti-coagulant. The tubes were centrifuged for 15 minutes at 240G to obtain a platelet-rich plasma (PRP) to which 300 ng/ml prostacyclin was added to stabilize the platelets during the washing procedure. Red cell free PRP was obtained by centrifugation for 10 minutes at 125G followed by further centrifugation for 15 minutes at 640G. The supernatant was discarded and the platelet pellet resuspended in modified, Calcium Free Tyrode solution (10 ml) (CFT), composition: NaCl 137mM, $NaHCO_3$ 11.9mM, NaH_2PO_4 0.4mM, KCl 2.7 mM, $MgCl_2$ 1.1 mM, dextrose 5.6 mM, gassed with 95% O_2/5% CO_2 and maintained at 37°C. Following addition of a further 300 ng/ml PGI_2, the pooled suspension was centrifuged once more for 15 minutes at 640G. The supernatant was discarded and the platelets resuspended initially in 10 ml CFT with further CFT added to adjust the final platelet count to $2x10^5$/ml. This final suspension was stored in a 60 ml syringe at 3°C with air excluded. To allow recovery from PGI_2-inhibition of normal function, platelets were used in aggregation studies no sooner than 2 hours after final resuspension.

In all studies, 3 ml aliquots of platelet suspension were added to tubes containing $CaCl_2$ solution (60 µl of 50 mM solution with a final concentration of 1mM). Human fibrinogen (Sigma, F 4883) and 8-sulphophenyltheophylline (8-SPT which was used to block any P_1-agonist activity of compounds) were added to give final concentrations of 0.2 mg/ml (60 µl of 10 mg/ml solution of clottable protein in saline) and 300 nM (10 µl of 15 mM solution in 6% glucose), respectively. Platelets or buffer as appropriate were added in a volume of 150 µl to the individual wells of a 96 well plate. All measurements were made in triplicate in platelets from each donor.

The agonist/antagonist potency was assessed as follows.

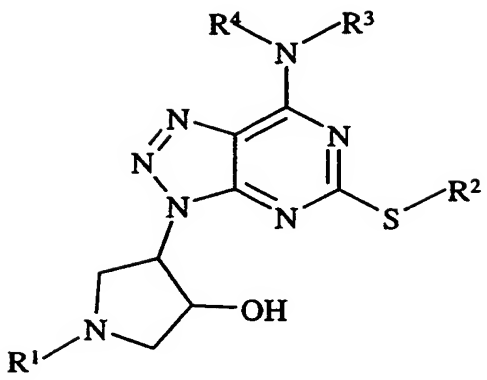
Aggregation responses in 96 well plates were measured using the change in absorbance given by the plate reader at 660 nm. Either a Bio-Tec Ceres 900C or a Dynatech MRX were used as the plate reader.

The absorbance of each well in the plate was read at 660 nm to establish a baseline figure. Saline or the appropriate solution of test compound was added to each well in a volume of 10 µl to give a final concentration of 0, 0.01, 0.1, 1, 10 or 100 mM. The plate was then shaken for 5 min on an orbital shaker on setting 10 and the absorbance read at 660 nm. Aggregation at this point was indicative of agonist activity of the test compound. Saline or ADP (30 mM; 10 µl of 450 mM) was then added to each well and the plate shaken for a further 5 min before reading the absorbance again at 660 nm.

Antagonist potency was estimated as a % inhibition of the control ADP response to obtain an IC_{50}. Compounds exemplified have pIC_{50} values of more than 5.0.

Claims

1. A compound of formula (I):



(I)

wherein:

R^1 is H, CH_2R^5 or COR^6;

R^2 is alkyl C_{1-6} or alkenyl C_{1-6}, optionally substituted by one or more groups selected from alkyl C_{1-6}, halogen;

R^3 is cycloalkyl C_{3-8}, optionally substituted by R^7;

R^4 is H or alkyl C_{1-6}, optionally substituted by one or more halogens;

R^5 is H, phenyl or alkyl C_{1-6}, optionally substituted by halogen, OR^8, phenyl;

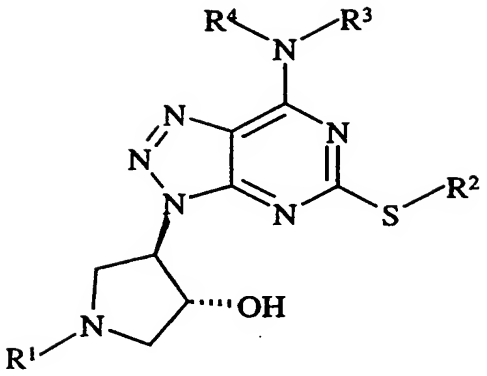
R^6 is OR^9 or alkyl C_{1-6}, optionally substituted by one or more groups selected from halogen, OR^{10}, phenyl;

R^7 is phenyl, optionally substituted by one or more groups selected from alkyl C_{1-6}, halogen, OR^8;

R^8, R^9 and R^{10}, are independently H or alkyl C_{1-6}, optionally substituted by one or more groups selected from halogen or alkyl C_{1-6};

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt

2. A compound according to claim 1 which is:



(Ia)

where R^1, R^2, R^3 and R^4 are as defined in claim 1.

3. A compound according to claim 2 in which R^3 is  where R^7 is as defined in claim 1.

4. A compound according to any one of claims 1 to 3 in which R^1 is H, CH_2Ph, CH_2CH_2OH, or CO_2tBu.

5. A compound according to any one of claims 1 to 4 in which R^2 is n-Pr.

6. A compound according to any one of claims 1 to 5 in which R^3 is cycloalkyl C_{3-8} substituted by phenyl.

7. A compound according to any one of claims 1 to 6 in which R^4 is H or methyl.

8. A compound according to claim 1 which is:
[3*R*-[3α,4β(1*R**,2*S**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol;

[3*S*-[3α,4β(1*S**,2*R**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester;

[3*S*-[3α,4β(1*R**, 2*S**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester;

[3*S*-[3α,4β(1*S**,2*R**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol;

[3*R*-[3α,4β(1*R**,2*S**)]]-4-[7-[*N*-Methyl-*N*-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol;

[3*R*-[3α,4β(1*R**,2*S**)]]-1-Hydroxyethyl-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol;

[3*R*-[3α,4β(1*R**,2*S**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-(phenylmethyl)-3-pyrrolidinol;

[3*R*-[3α, 4β(1*R**,2*S**)]]-1-Acetyl-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol.

Or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 8 in combination with a pharmaceutically acceptable diluent, adjuvent or carrier.

10. A pharmaceutical composition for use in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease, comprising a compound according to any one of claims 1 to 8.

11. A pharmaceutical composition for use in the treatment or prevention of unstable or stable angina, comprising a compound according to any one of claims 1 to 8.

12. A compound according to any one of claims 1 to 8 for use in therapy.

13. A compound according to any one of claims 1 to 8 for use in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease.

14. A compound according to any one of claims 1 to 8 for use in the treatment or prevention of unstable or stable angina.

15. The use of a compound according to any one of claims 1 to 8 as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease.

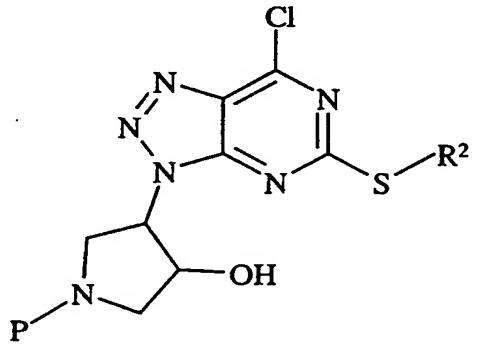
16. The use of a compound according to any one of claims 1 to 8 as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of unstable or stable angina

17. A method of treatment or prevention of a platelet aggregation disorder which comprises administering to a person suffering from or susceptible to such a disorder a therapeutically effective amount of compound according to any one of claims 1 to 8.

18. A method of treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease, which comprises administering to a person suffering from or susceptible to such a disorder a therapeutically effective amount of a compound according to any one of claims 1 to 8.

19. A method of treatment or prevention of unstable or stable angina, which comprises administering to a person suffering from or susceptible to such a disorder a therapeutically effective amount of a compound according to any one of claims 1 to 8.

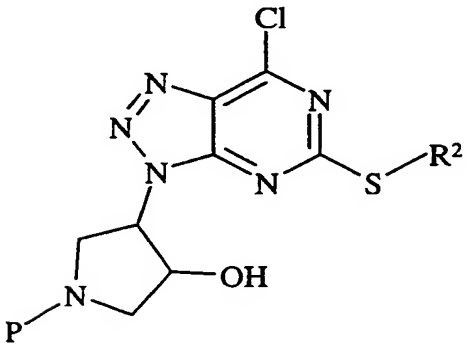
20. A process for the preparation of a compound of formula (I), where R^1 is H, which comprises reacting a compound of formula (II):



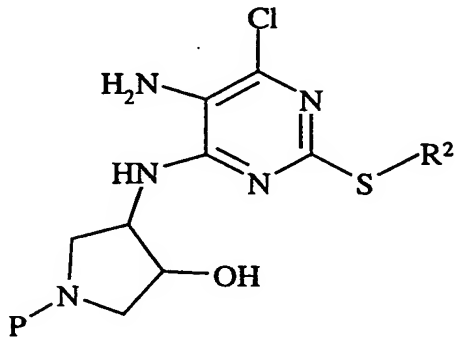
(II)

wherein R^2 is as defined in claim 1 and P is a protecting group, with R^3R^4NH, wherein R^3 and R^4 are as defined in claim 1, and a base and optionally thereafter removing any protecting groups.

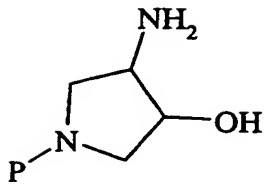
21. Compounds of formula (II), (III), (IV) and (V):



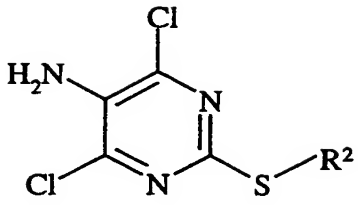
(II)



(III)



(IV)



(V)

wherein R^2 is as defined in claim 1 and P is a protecting group.

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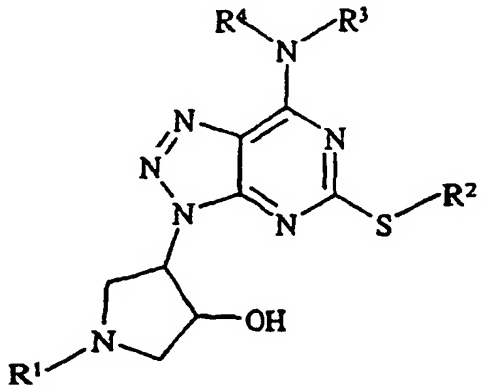
(54) Title: TRIAZOLOPYRIMIDINE DERIVATIVES



(I)

(57) Abstract: Compounds of the formula (I) and their use as anti-platelet aggregation compounds.

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INTERNATIONAL SEARCH REPORT

[redacted] tional Application No
PCT/GB 00/03474

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/519 A61P9/00 C07D403/12 C07D207/14
C07D239/46 //(C07D487/04,249:00,239:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, WPI Data, BEILSTEIN Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	YEN-SHI LAI ET AL.: "Synthesis and protei kinase C inhibitory activities of lanol anaogs with replacement of the perhydroazepine moiety" JOURNAL OF MEDICINAL CHEMISTRY., vol. 40, no. 2, 1997, pages 226-35, XP002162230 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 compound 18 --- -/--	21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 March 2001	28/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

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INTERNATIONAL SEARCH REPORT

[illegible] tional Application No
PCT/GB 00/03474

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELE[illegible]

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